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Smoking and Mouth-Throat Cancer

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A CAUSAL RELATIONSHIP between smoking and squamous carcinoma of the lung has been generally accepted in the past few years. Such a cause-and-effect relationship between tobacco and cancer of the mouth and throat* has, however, not been firmly established, except for larynx and lip cancers [1]. The infrequency of cancer in certain oropharyngeal sites makes it difficult to amass sufficient numbers of cases to satisfy statistical criteria, such as has been done in the large retrospective and prospective studies on the more common cancer of the lung. There is, however, another type of study possible in the oropharyngeal cancer area which may shed light on the role of tobacco from a new and hitherto unexplored standpoint; it is the subject of this communication.

Earlier work on the effect of cigarette smoke condensate on various animal tissues led us to recognize the key role in carcinogenesis played by the accessory structures of a surface epithelium, such as the pilosebaceous apparatus of the skin, and the mucus glands of the oral mucosa [2,3]. Study of the mucus-producing epithelium from various sites in the human mouth and throat where squamous carcinoma arises demonstrates surprising similarity of microscopic structure, although the gross anatomy varies greatly. And so, in the following study, we intend to consider as a group all the squamous carcinomas arising from the mucosa of the mouth, pharynx and larynx, a mucosa that is similar not only in cellular structure but also in being a surface that is in contact with tobacco or smoke in any smoker, chewer or snuffer.

Over a period of twelve years we have noted the dismaying frequency of second, new squamous carcinomas of the mouth-throat region, usually several years after control of the first such cancer. And the second one would often kill the patient. (That we were dealing here with new cancers, not recurrences, will be taken up later.) Soon it was apparent that these second cancers usually occurred in patients who continued to smoke. Further study seemed needed, and when this was done, the distribution of second cancers among continuing smokers and those who quit smoking suggested a new approach to the study of the association of tobacco with mouth and throat cancer.

* Throat refers to pharynx, hypopharynx, extrinsic and intrinsic larynx (glottic and extraglottic).

MATERIALS AND METHODS

During the years 1953 through 1960, we saw roughly 400 patients with mouth and throat cancers in the office and in the tumor clinic of the Louisville General Hospital. Many were treated elsewhere before coming; many were untreatable when first seen. Since we are not interested here in survival rates, the exact number is unimportant. Over 90 per cent of these patients were adequately followed, and of these, ninety-five patients with squamous carcinoma (or its histologic variants) of the mouth or throat were found living and well for three years or more after treatment. In eighty-five of these patients a satisfactory smoking history was obtained by us and one other trained person (tumor clinic secretary). The follow-up period in the eighty-five patients averaged 6.8 years.

We arbitrarily chose the three year disease free interval as a criterion in the selection of this group in order to avoid confusing recurrence with a new primary cancer. A three year disease-free interval gives moderate assurance of control in mouth-throat cancer [4]. Also, three years was chosen as allowing sufficient time for smoking effect on tissues to wear off or revert toward normal, if indeed this could happen, in patients who quit smoking.

Of the eighty-five patients thoroughly documented for this study, seven had never smoked or used tobacco in any form. Obviously their cancers had causes other than tobacco and they were excluded from the group. It is of interest that none of these

FIG. 1. Specimen of a patient with cancer of the right pyriform sinus with neck metastasis. He switched from cigarettes to pipe and cigars after laryngectomy. Six years later, he developed extensive "cancerization" of pharynx, and at eight years multiple cancers of the soft palate.

TABLE I

SEVENTY-EIGHT PATIENTS* LIVING AND WELL > THREE YEARS

Sex:	Male: female ratio = 2.5:1
Age:	Mean = 57.6 yr.
Amount smoked:	Mean = 1.39 packages of cigarettes/day (based on all 66 of 78 who smoked cigarettes at all)
Type of tobacco:	56 pure cigarette smokers; 5 pure pipe smokers; 1 pure chewer; 1 pure snuffer; 15 used various combinations
Length of time smoked:	Mean = 36.4 yr.
Site of primary cancers:	Larynx (int. & ext.) 22; floor of mouth, 20; tongue, 14; palate, 9; gum, 6; buccal mucosa, 4; tonsil, 3
Treatment:	Surgery, 35; radiation, 14; both, 29
Length of follow-up:	Mean = 6.7 yr.

* All used tobacco.

seven developed second mouth-throat cancers although, if the unknown factors operating to produce their cancers were to continue, there is no reason why they may not get second cancers.

This final group of seventy-eight patients was then divided into two subgroups: those who quit smoking and those who continued to smoke after their first cancer. And finally, note was made of those among the seventy-eight who developed second, new mouth or throat cancers.

Several patients developed possible second cancers in less than three years; but because of doubt as to whether or not they were recurrences, they were not counted as second cancers. We excluded lip cancer from our study because of the possibly confusing effect of sunlight on its genesis. Several patients developed middle or lower esophageal cancer three or more years after their mouth or throat cancer; these were not counted as second, new cancers since the esophagus may not often be in direct contact with tobacco or smoke. Only one second cancer arose in the same anatomic site as the first one in our material; however, several patients had more than two cancers, and the palate was sometimes the seat of multiple cancers. Data on the group of seventy-eight are seen in Table I.

RESULTS

The final group of seventy-eight patients, all of whom had used tobacco moderately to heavily, all of whom had been "cured" of one mouth-throat cancer, *divided themselves* into two subgroups after their first cancer: (1) those who quit smoking, twenty-nine patients; (2) those who continued to smoke, forty-nine patients. These two groups are comparable in a number of respects. (Table II.)

Eighteen patients of the seventy-eight developed a second tobacco-area squamous cancer with an average interval of 5.7 years between the cancers. Seventeen of these second cancers occurred in the patients who continued to smoke (Fig. 1 to 4); only one appeared among

TABLE II

COMPARISON OF TWO GROUPS

	Quit Smoking—29	Continued Smoking—49
Sex: Male: female ratio	2.6:1	2.5:1
Age: Mean	58.5 yr.	57 yr.
Amount smoked: Mean	1.41 pkg. cigarettes/day (22 pts.—1 pkg./day or more) (6 pts.—2 pkg./day or more)	1.37 pkg. cigarettes/day (35 pts.—1 pkg./day or more) (6 pts.—2 pkg./day or more)
Length time smoked: Mean	32.4 yr.	38.7 yr.
Median	33.5 yr.	36.5 yr.
Second cancers:	1	17

FIG. 2. Same patient as Figure 1. He has now quit smoking, is well at eleven years. (Plastic laryngectomy button was invented by him, keeps open a contracted stoma.)

the subgroup that had quit tobacco. This one developed two and a half years after the first cancer, but we believed it was close enough to the arbitrary three year interval to justify inclusion.

The difference in distribution of second cancers between the two subgroups is highly significant ($P = .0018$), if one accepts that the subgroups are reasonably homogeneous and comparable in other respects. Data on the eighteen patients with second cancers appears in Table III.

COMMENTS

To our knowledge this is a unique type of study regarding human cancer and a possible external carcinogen. Previous investigations have compared one group of patients who develop cancer with a second group who do not, as to amount of exposure to an external agent; or often epidemiologists compare a group not exposed to an agent with a group exposed and total the number of cancers that develop in the two. In such groupings the factors of innate susceptibility to cancer, whatever

TABLE III

EIGHTEEN PATIENTS WHO DEVELOPED SECOND CANCERS

Number of patients in "quit" group:	1
Number of patients in "continued" group:	17
Sex:	Males, 10; females, 8
Age:	Mean = 55 yr.
Amount smoked:	Mean = 1.30 pkg. cigarettes/day (15 pure cigarette smokers; 2 pipe-cigar smokers; 1 pure snuffer)
Reduction of smoking:	1 pt. significantly reduced smoking after first cancer; (9 pts. of the remaining 32 significantly reduced)
Length of time smoked:	Mean = 35.2 yr.
Interval between cancers:	Mean = 5.7 yr.
First cancer site:	Floor of mouth, 10; palate, 3; tongue, 3; gum, 1; larynx, 1
Second cancer site:	Larynx, 4; palate, 3; buccal mucosa, 3; tongue, 2; lung, 2; pharynx, 2; cervical esophagus, 1; gum, 1

FIG. 3. Cancer of right lateral tongue, treated surgically. This woman continued cigarettes. Five years later she developed a tiny cancer on the opposite lateral tongue border.

FIG. 4. Cancer of the floor of the mouth. Patient continued cigarettes. Nine years later he developed cancer of larynx.

these may be, are not considered or equalized, thus leaving to chance distribution a vast number of influences that may play important roles, such as genetic determinants, viral resistance forces or hormone imbalances, to mention a few. This present study attempts to equalize such factors by including only patients who have already had cancer. Every one is, therefore, cancer-susceptible and, more particularly, susceptible in a single tissue of the body. In this regard our patients may be more homogeneous than an inbred strain of laboratory animals. But, of course, in many respects the patients may vary widely; we have no data on race, alcoholic intake, diet, weight or previous syphilis, for instance.

The two subgroups definitely vary in the mean length of time smoked, 32.4 years as compared to 38.7 years. One might well believe that the second cancers naturally occurred in those whose mucosae had been exposed the longest. Yet further analysis reveals that only five patients caused the major difference between the subgroups: five patients in the "quit" group had smoked less than twenty years, whereas no patients in the "continued" group had smoked less than twenty years. Without these five, figures for the two subgroups come out quite close to each other: 36.8 years and 38.7 years. Obviously five atypical individuals in the group of twenty-nine could not explain the second cancer distribution.

It was fortunate that a fair segment of patients quit tobacco so as to give two subgroups to compare. One cannot very well plan to manipulate patients in this manner. The result of stopping smoking then appears to confer remarkable protection against mouth-throat cancer. How can this be reconciled with the only very modest protection against lung cancer calculated for those who quit [1]? First of all, lung studies are constructed differently from this one and are, therefore, not comparable. Secondly, there may well be a difference in tissue susceptibility between the mouth-throat and the lung. The greater incidence of lung cancer suggests a greater sensitivity of lung mucosa to smoking; and this, in turn, suggests a longer *reversible* precancerous stage in mouth and throat mucosa, which would yield a greater result from quitting. Thirdly, most lung cancer patients do not live to acquire mouth-throat cancer, if they were destined to; fourthly, new lung lesions are probably considered to be metastases rather than new, second cancers. Finally, protection by quitting may be somehow enhanced in our series by the fact that the mouth-throat area most severely affected by tobacco has been excised or heavily radiated before the study begins. Therefore, only the other, less tobacco-assaulted areas of mucosa remain to develop cancer, which may take quite a long time.

That radiation is not causing these second cancers seems evident from the equal distribution of radiated patients in the two subgroups (data not included in tables).

The three year interval chosen in this study is not a magic one and serves only to set some limit within which to begin the study. Second cancers will certainly develop occasionally in any patient and at any time. Several of these patients probably had second cancers within two years, but they were not so counted for reasons mentioned above. One patient seen recently with mouth cancer had quit smoking completely one year before. No absolute protection results from quitting, in all probability, but a highly worthwhile degree of protection seems likely. The implication is that a patient whose mucosa survives without cancer for three years is very unlikely to get cancer there without further tobacco application.

Such a relationship as here described suggests that tobacco may act as a promoter rather than a carcinogen *per se*. Both types of action have been found in the various polycyclic hydrocarbons in tobacco. From a clinical standpoint, however, this is quibbling if the withholding of an external substance can control the major incidence of the disease.

Is it possible that some factor other than quitting or continuing smoking accounts for the second cancer distribution? Obviously it is possible, but we have no inkling of what the factor could be. Race, alcoholic intake, diet, family history and all known such items are too loosely associated with mouth-throat cancer to account for such a marked difference, as far as present knowledge goes.

Is this study a demonstration of a reversible precancerous state in the oral mucosa? Probably so, in many cases. In addition there must be many patients with early cellular changes that will not progress further toward cancer without further external carcinogenic stimulus. In these we need not reverse the process but

merely hold it stationary in order to protect the patient's health.

Are we justified in concluding that tobacco causes mouth-throat cancer? The numbers of the subgroups are quite small and the number of uncontrolled variables in any human groupings necessarily numerous; therefore, few will consider the causal connection as proved. Furthermore, any serious concept of cancer causation must include a multitude of factors acting together, of which an external chemical agent can only be one. However, the figures strongly suggest that tobacco is a *determining* factor in mouth-throat cancer, without which relatively few such cancers would develop.

SUMMARY AND CONCLUSIONS

1. A group of "cured" mouth-throat cancer patients divided themselves into two subgroups: those who quit smoking and those who continued to smoke after having cancer.

2. These two subgroups are comparable in most parameters studied.

3. In a mean follow-up time of 6.7 years, and at least three years after their first cancer, seventeen of forty-nine who continued to smoke developed a second mouth-throat cancer, while only one of twenty-nine who had quit smoking developed a second cancer.

4. This significant difference in incidence of second cancers adds evidence to support a causal relation of tobacco with mouth-throat cancer.

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